

Amendments to the Claims:

This listing of claims replaces all prior versions and listings of claims in the application:

Listing of Claims:

1. (Original) An antibody comprising a single-chain polypeptide having binding activity against TPO receptor (Mpl), wherein said antibody comprises two heavy chain variable regions and two light chain variable regions.

2. (Original) The antibody of claim 1, wherein the two heavy chain variable regions and the two light chain variable regions are arranged in the order of heavy chain variable region, light chain variable region, heavy chain variable region, and light chain variable region from the N terminus of the single-chain polypeptide.

3. (Previously Presented) The antibody of claim 1, wherein the two heavy chain variable regions and the two light chain variable regions are linked by linkers.

4. (Original) The antibody of claim 3, wherein the linkers comprise 15 amino acids.

5. (Original) A chimeric antibody that binds to Mpl.

6. (Original) The antibody of claim 5, which is a humanized antibody.

7. (Previously Presented) The antibody of claim 5, which is a minibody.

8. (Original) An antibody that binds to soluble Mpl.

9. (Withdrawn) An antibody that binds to human Mpl and monkey Mpl.
10. (Withdrawn) An antibody having agonistic activity against human Mpl and monkey Mpl.
11. (Original) An antibody whose binding activity to soluble Mpl is  $KD = 10^{-6}$  M or lower.
12. (Original) An antibody whose binding activity to soluble Mpl is  $KD = 10^{-7}$  M or lower.
13. (Original) An antibody whose TPO agonistic activity is  $EC50 = 100$  nM or lower.
14. (Original) An antibody whose TPO agonistic activity is  $EC50 = 30$  nM or lower.
15. (Original) An antibody whose TPO agonistic activity is  $EC50 = 10$  nM or lower.
16. (Currently Amended) The antibody of claim 32 that comprises a heavy chain variable region, wherein said heavy chain variable region comprises CDR1, CDR2 and CDR3 consisting of an amino acid sequence of any one of:
  - ~~[1]~~ (a) SEQ ID NOs: 3, 4, and 5
  - ~~[2]~~ (b) SEQ ID NOs: 6, 7, and 8
  - ~~[3]~~ (c) SEQ ID NOs: 9, 10, and 11
  - ~~[4]~~ (d) SEQ ID NOs: 15, 16, and 17
  - ~~[5]~~ (e) SEQ ID NOs: 18, 19, and 20
  - ~~[6]~~ (f) SEQ ID NOs: 21, 22, and 23
  - ~~[7]~~ (g) SEQ ID NOs: 24, 25, and 26

- {8} (h) SEQ ID NOs: 27, 28, and 29
- {9} (i) SEQ ID NOs: 30, 31, and 32
- {10} (j) SEQ ID NOs: 33, 34, and 35
- {11} (k) SEQ ID NOs: 36, 37, and 38
- {12} (l) SEQ ID NOs: 39, 40, and 41
- {13} (m) SEQ ID NOs: 42, 43, and 44
- {14} (n) SEQ ID NOs: 48, 49, and 50
- {15} (o) SEQ ID NOs: 51, 52, and 53
- {16} (p) SEQ ID NOs: 54, 55, and 56
- {17} (q) SEQ ID NOs: 57, 58, and 59.

17. (Currently Amended) The antibody of claim 32 that comprises a light chain variable region, wherein said light chain variable region comprises CDR1, CDR2 and CDR3 consisting of an amino acid sequence of any one of:

- {1} (a) SEQ ID NOs: 60, 61, and 62
- {2} (b) SEQ ID NOs: 63, 64, and 65
- {3} (c) SEQ ID NOs: 78, 79, and 80
- {4} (d) SEQ ID NOs: 84, 85, and 86
- {5} (e) SEQ ID NOs: 93, 94, and 95
- {6} (f) SEQ ID NOs: 96, 97, and 98
- {7} (g) SEQ ID NOs: 102, 103, and 104
- {8} (h) SEQ ID NOs: 108, 109, and 110
- {9} (i) SEQ ID NOs: 111, 112, and 113
- {10} (j) SEQ ID NOs: 114, 115, and 116.

18. (Currently Amended) The antibody of claim 32 that comprises a heavy chain variable region and a light chain variable region of any one of:

{1} (a) a heavy chain variable region that comprises CDR1, CDR2, and CDR3 comprising the amino acid sequences consisting of SEQ ID NOs: 3, 4, and 5, and a light chain variable region that comprises CDR1, CDR2, and CDR3 comprising the amino acid sequences consisting of SEQ ID NOs: 60, 61, and 62;

{2} (b) a heavy chain variable region that comprises CDR1, CDR2, and CDR3 comprising the amino acid sequences consisting of SEQ ID NOs: 6, 7, and 8, and a light chain variable region that comprises CDR1, CDR2, and CDR3 comprising the amino acid sequences consisting of SEQ ID NOs: 63, 64, and 65;

{3} (c) a heavy chain variable region that comprises CDR1, CDR2, and CDR3 comprising the amino acid sequences consisting of SEQ ID NOs: 9, 10, and 11, and a light chain variable region that comprises CDR1, CDR2, and CDR3 comprising the amino acid sequences consisting of SEQ ID NOs: 63, 64, and 65;

{4} (d) a heavy chain variable region that comprises CDR1, CDR2, and CDR3 comprising the amino acid sequences consisting of SEQ ID NOs: 15, 16, and 17, and a light chain variable region that comprises CDR1, CDR2, and CDR3 comprising the amino acid sequences consisting of SEQ ID NOs: 63, 64, and 65;

{5} (e) a heavy chain variable region that comprises CDR1, CDR2, and CDR3 comprising the amino acid sequences consisting of SEQ ID NOs: 18, 19, and 20, and a light chain variable region that comprises CDR1, CDR2, and CDR3 comprising the amino acid sequences consisting of SEQ ID NOs: 63, 64, and 65;

{6} (f) a heavy chain variable region that comprises CDR1, CDR2, and CDR3 comprising the amino acid sequences consisting of SEQ ID NOs: 21, 22, and 23, and a light chain variable region that comprises CDR1, CDR2, and CDR3 comprising the amino acid sequences consisting of SEQ ID NOs: 78, 79, and 80;

{7} (g) a heavy chain variable region that comprises CDR1, CDR2, and CDR3 comprising the amino acid sequences consisting of SEQ ID NOs: 24, 25, and 26, and a light chain variable region that comprises CDR1, CDR2, and CDR3 comprising the amino acid sequences consisting of SEQ ID NOs: 63, 64, and 65;

{8} (h) a heavy chain variable region that comprises CDR1, CDR2, and CDR3 comprising the amino acid sequences consisting of SEQ ID NOs: 27, 28, and 29, and a light chain variable region that comprises CDR1, CDR2, and CDR3 comprising the amino acid sequences consisting of SEQ ID NOs: 84, 85, and 86;

{9} (i) a heavy chain variable region that comprises CDR1, CDR2, and CDR3 comprising the amino acid sequences consisting of SEQ ID NOs: 30, 31, and 32, and a light chain variable region that comprises CDR1, CDR2, and CDR3 comprising the amino acid sequence consisting of SEQ ID NOs: 63, 64, and 65;

{10} (j) a heavy chain variable region that comprises CDR1, CDR2, and CDR3 comprising the amino acid sequences consisting of SEQ ID NOs: 33, 34, and 35, and a light chain variable region that comprises CDR1, CDR2, and CDR3 comprising the amino acid sequences consisting of SEQ ID NOs: 63, 64, and 65;

{11} (k) a heavy chain variable region that comprises CDR1, CDR2, and CDR3 comprising the amino acid sequences consisting of SEQ ID NOs: 36, 37, and 38, and a light chain variable region that comprises CDR1, CDR2, and CDR3 comprising the amino acid sequences consisting of SEQ ID NOs: 93, 94, and 95;

{12} (l) a heavy chain variable region that comprises CDR1, CDR2, and CDR3 comprising the amino acid sequences consisting of SEQ ID NOs: 39, 40, and 41, and a light chain variable region that comprises CDR1, CDR2, and CDR3 comprising the amino acid sequences consisting of SEQ ID NOs: 96, 97, and 98;

{13} (m) a heavy chain variable region that comprises CDR1, CDR2, and CDR3 comprising the amino acid sequences consisting of SEQ ID NOs: 42, 43, and 44, and a light chain variable region that comprises CDR1, CDR2, and CDR3 comprising the amino acid sequences consisting of SEQ ID NOs: 78, 79, and 80;

{14} (n) a heavy chain variable region that comprises CDR1, CDR2, and CDR3 comprising the amino acid sequences consisting of SEQ ID NOs: 45, 46, and 47, and a light chain variable region that comprises CDR1, CDR2, and CDR3 comprising the amino acid sequences consisting of SEQ ID NOs: 102, 103, and 104;

{H5} (o) a heavy chain variable region that comprises CDR1, CDR2, and CDR3 comprising the amino acid sequences consisting of SEQ ID NOs: 48, 49, and 50, and a light chain variable region that comprises CDR1, CDR2, and CDR3 comprising the amino acid sequences consisting of SEQ ID NOs: 63, 64, and 65;

{H6} (p) a heavy chain variable region that comprises CDR1, CDR2, and CDR3 comprising the amino acid sequences consisting of SEQ ID NOs: 51, 52, and 53, and a light chain variable region that comprises CDR1, CDR2, and CDR3 comprising the amino acid sequences consisting of SEQ ID NOs: 108, 109, and 110,

{H7} (q) a heavy chain variable region that comprises CDR1, CDR2, and CDR3 comprising the amino acid sequences consisting of SEQ ID NOs: 54, 55, and 56, and a light chain variable region that comprises CDR1, CDR2, and CDR3 comprising the amino acid sequences consisting of SEQ ID NOs: 111, 112, and 113;

{H8} (r) a heavy chain variable region that comprises CDR1, CDR2, and CDR3 comprising the amino acid sequences consisting of SEQ ID NOs: 57, 58, and 59, and a light chain variable region that comprises CDR1, CDR2, and CDR3 each comprising the amino acid sequences consisting of SEQ ID NOs: 114, 115, and 116.

19. (Previously Presented) The antibody of claim 32 that comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 118.

20. (Previously Presented) The antibody of claim 32 that comprises a light chain variable region comprising the amino acid sequence of SEQ ID NO: 120.

21. (Previously Presented) The antibody of claim 32 that comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 118 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 120.

22. (Previously Presented) The antibody of claim 32 that comprises the amino acid sequence of SEQ ID NO: 122 or 264.

23. (Currently Amended) The antibody of claim 16, wherein said heavy chain variable region comprises FR1, FR2, FR3, and FR4 consisting of amino acid sequences of any one of:

~~{1}~~ (a) SEQ ID NOs: 230, 232, 234, and 236

~~{2}~~ (b) SEQ ID NOs: 265, 267, 269, and 271

~~{3}~~ (c) SEQ ID NOs: 279, 281, 283, and 285

~~{4}~~ (d) SEQ ID NOs: 298, 299, 300, and 301

~~{5}~~ (e) SEQ ID NOs: 298, 299, 306, and 301.

24. (Currently Amended) The antibody of claim 17, wherein said light chain variable region comprises FR1, FR2, FR3, and FR4 consisting of amino acid sequences of any one of:

~~{1}~~ (a) SEQ ID NOs: 239, 241, 243, and 245

~~{2}~~ (b) SEQ ID NOs: 272, 274, 276, and 278

~~{3}~~ (c) SEQ ID NOs: 302, 303, 304, and 305

~~{4}~~ (d) SEQ ID NOs: 302, 307, 308, and 305.

25. (Currently Amended) The antibody of claim 18 that comprises a heavy chain variable region and a light chain variable region of any one of:

~~{1}~~ (a) a heavy chain variable region which comprises FR1, FR2, FR3, and FR4 having the amino acid sequences consisting of SEQ ID NOs: 230, 232, 234, and 236, and a light chain variable region which comprises FR1, FR2, FR3, and FR4 having the amino acid sequences consisting of SEQ ID NOs: 239, 241, 243, and 245;

~~{2}~~ (b) a heavy chain variable region which comprises FR1, FR2, FR3, and FR4 having the amino acid sequences consisting of SEQ ID NOs: 265, 267, 269, and 271, and a light chain variable region which comprises FR1, FR2, FR3, and FR4 having the amino acid sequences consisting of SEQ ID NOs: 272, 274, 276, and 278;

{3} (c) a heavy chain variable region which comprises FR1, FR2, FR3, and FR4 having the amino acid sequences consisting of SEQ ID NOs: 279, 281, 283, and 285, and a light chain variable region which comprises FR1, FR2, FR3, and FR4 having the amino acid sequences consisting of SEQ ID NOs: 272, 274, 276, and 278;

{4} (d) a heavy chain variable region which comprises FR1, FR2, FR3, and FR4 having the amino acid sequences consisting of SEQ ID NOs: 298, 299, 300, and 301, and a light chain variable region which comprises FR1, FR2, FR3, and FR4 having the amino acid sequences consisting of SEQ ID NOs: 302, 303, 304, and 305;

{5} (e) a heavy chain variable region which comprises FR1, FR2, FR3, and FR4 having the amino acid sequences consisting of SEQ ID NOs: 298, 299, 306, and 301, and a light chain variable region which comprises FR1, FR2, FR3, and FR4 having the amino acid sequences consisting of SEQ ID NOs: 302, 307, 308, and 305.

26. (Previously Presented) The antibody of claim 32 that comprises a heavy chain variable region, wherein said heavy chain variable region comprises the amino acid sequence of SEQ ID NO: 229, 256, 262, 289, or 295.

27. (Previously Presented) The antibody of claim 32 that comprises a light chain variable region, wherein said light chain variable region comprises the amino acid sequence of SEQ ID NO: 238, 258, 291, or 297.

28. (Currently Amended) The antibody of claim 32 that comprises a heavy chain variable region and a light chain variable region of any one of:

{H} (a) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 229, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 238;

{2} (b) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 256, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 258;



~~{3}~~ (c) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 262, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 258;

~~{4}~~ (d) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 289, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 291;

~~{5}~~ (e) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 295, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 297.

29. (Previously Presented) The antibody of claim 32 that comprises the amino acid sequence of SEQ ID NO: 2, 254, 260, 287, or 293.

30.-31. (Canceled)

32. (Original) An antibody that recognizes the region of amino acids 26 to 274 of human Mpl.

33. (Previously Presented) An antibody of claim 1, which has TPO agonistic activity.

34. (Withdrawn) A polynucleotide encoding an antibody of claim 1.

35. (Withdrawn) A polynucleotide hybridizing to the polynucleotide of claim 34 under stringent conditions, wherein said polynucleotide encodes an antibody having binding activity against TPO receptor (Mpl).

36. (Withdrawn) A vector comprising the polynucleotide of claim 34.

37. (Withdrawn) A host cell that carries the polynucleotide of claim 34.

38. (Previously Presented) A pharmaceutical composition comprising an antibody of claim 32.

39. (Withdrawn) The antibody of claim 32, wherein the antibody recognizes an epitope recognized by an antibody consisting of the amino acid sequence of SEQ ID NO:2.

40. (Withdrawn) The antibody of claim 32, wherein the antibody recognizes an epitope within the region of amino acids 189 to 245 of human Mpl.

41. (Withdrawn) The antibody of claim 32, wherein the antibody recognizes an epitope within the region of amino acids 213 to 231 of human Mpl.

42. (Previously Presented) The antibody of claim 32, wherein the antibody comprises a heavy chain variable region containing a CDR1 amino acid sequence of SEQ ID NO:36 in which one or more amino acid residues has been substituted, deleted, added, and/or inserted; a CDR2 amino acid sequence of SEQ ID NO:37 in which one or more amino acid residues has been substituted, deleted, added, and/or inserted; and a CDR3 amino acid sequence of SEQ ID NO:38 in which one or more amino acid residues has been substituted, deleted, added, and/or inserted, wherein the antibody has an activity of a second antibody whose heavy chain variable region comprises SEQ ID NOs:36, 37 and 38 and whose light chain variable region SEQ ID NOs:93, 94 and 95.

43. (Previously Presented) The antibody of claim 42, wherein the antibody binds to the same epitope as the second antibody.